

A. Dempski

Dempski's discovery of a controlled release form of carbidopa-levodopa was a major therapeutic advance in the treatment of Parkinson's disease. It stabilized plasma levodopa levels, reduced neurologic and gastrointestinal side effects and increased the duration of antiparkinson activity. However, Dempski's formulation was flawed by a serious 2-hour delay in the onset of action of carbidopa-levodopa. The present invention corrects this flaw via bilayer tablet formulations which provide rapid onset and sustained therapeutic action, a clear clinical advantage for the Parkinson patient in need of expeditious symptomatic control. Moreover, Dempski teaches a single layered tablet, a sustained release profile and excipients which support that profile. The present invention teaches a bilayer tablet consisting of excipients known to those skilled in the art as possessing superior drug dissolution and disintegration properties (eg., croscarmellose sodium, microcrystalline cellulose) enhancing immediate release, and others, such as Methocel, which provide sustained release (Remington's Pharmaceutical Sciences 18<sup>th</sup> Edition, 1990 pp 1635-1637).

B. Conte

Conte's tablet formulations contain immediate and sustained release characteristics, but their medical utility in Parkinson's disease, their arrangement and symmetry, their composition, and their construction are significantly different from those elements of the present invention, as follows:

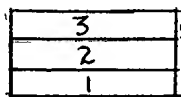
1. Medical Utility. Although Conte claims immediate and sustained release for the combination carbidopa-levodopa, it is likely that the actual immediate release profile is not adequate to satisfy targeted therapeutic needs in Parkinson's disease. For example, in example 3, column 11, table 3, it took 2 hours for immediate release ketoprofen to deliver just 50.2 per cent of drug substance, and 24 hours for 99.6 per cent release. A comparable "immediate" release pattern for carbidopa-levodopa would duplicate and even prolong Dempski's delayed onset deficiency and sacrifice medical utility. In the present invention, immediate release of carbidopa-levodopa refers to a rapid onset of action (0.5 hours) equivalent to that of the original marketed product (Physicians Desk Reference, 47<sup>th</sup> Edition p.976, 1993).

2. Three Layer vs Two Layer Tablets. Conte claims a 3-layer tablet consisting of a first layer containing immediate or controlled release drugs, a second layer containing one or more drugs either equal to or different from the first layer with slow release formulation and a third rate-controlling barrier layer containing drug, if necessary. Moreover, Conte's 3-layer tablet formulations are definitively cited (1) in a drawing on the title page that specifically labels layers 1, 2 and 3, (2) in figures 1 and 2 on the back of the title page that also illustrates and labels 3 layers in each figure, (3) in the Summary section of column 3, lines 17-28, (4) in the Detailed Description section of column 3, lines 38-46, (5) again in the Brief Description of the Drawing section, line 51-54, (6) in other locations in the Specifications and (7) in the Claims, where the 3-layer tablet is mentioned in all 7 claims. The present invention describes a 2-layer tablet consisting of a sustained release core overcoated only with an immediate release layer.

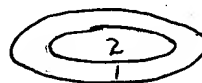
3. Multilayer Tablets. In addition to bilayer tablets, the multilayer

tablets of the present invention contain an excipient layer which, unlike Conte's third barrier layer, is drug-free and does not contain rate-controlling polymers. Conte's third layer contains 5-90 per cent by weight of various polymers (column 18, line 16) and if necessary, a drug (title page abstract).

4. Tablet Construction. Conte claims a tablet consisting of three discrete disc-shaped layers arranged adjacent to one another. Drug release characteristics are a function of exposure of each layer to an aqueous medium and are controlled, in part, by limited aqueous access imposed by the physical structure of the 3-layer tablet. Such limited access may contribute to impeded immediate release of certain drug substances such as the combination carbidopa-levodopa. Bilayer tablets of the present invention, on the other hand, consist of a core drug component overcoated by a drug layer which has total external surface exposure and exclusive availability for initial rapid therapeutic action (tablet cross sections below).



Conte Tablet



Present Invention Tablet

COMMENTS

Applicant's arguments have directly addressed the major prior art concerns of the examiner which state that the prior art teaches a "tablet formulation comprising a combination of carbidopa and levodopa formulations with immediate and sustained release rates and recognizes the treatment of Parkinson's disease by employing formulations of carbidopa and levodopa as instantly claimed".

The applicant claims in response that the prior art has critical shortcomings (corrected by the present invention) which subvert their utility as effective treatments for Parkinson's disease. For example, Dempski has no immediate release system in place to expeditiously reverse the debilitating symptoms experienced by Parkinson patients and Conte's immediate release system seems unable to provide sufficient drug substance in a timely fashion (see A, B1 above)

Moreover, unlike the tablet formulations of Dempski and Conte, those of the present invention are bilayered, configured for unimpeded immediate drug release and consist of excipients, known to those skilled in the art, which

accelerate immediate drug release and provide sustained therapeutic action (see A, B2, B3, B4 above).

### CLAIMS

24. A method for treating Parkinson's disease which provides rapid and sustained symptomatic relief, principally avoiding delay in therapeutic onset of action, by administering a bilayer tablet formulation consisting of an immediate release layer of 10-25 mg carbidopa and 50-200 mg levodopa and a sustained release layer of 25-75 mg carbidopa and 100-400 mg levodopa.

25. A method according to claim 24, the bilayer tablet consisting of a sustained release core layer of carbidopa-levodopa overcoated by an immediate release layer of carbidopa-levodopa.

26. The pharmaceutical composition of claim 25, wherein at least one sustained release layer of carbidopa-levodopa is separated from at least one immediate release layer of carbidopa-levodopa by an excipient layer which is drug-free and does not contain rate-controlling polymers.

27. A method according to claim 25, wherein said method avoids significant onset delay in effecting such treatment, said immediate release layer providing rapid onset of antiparkinson activity and said sustained release layer providing sustained antiparkinson activity.

28. A method according to claim 25, wherein said method avoids significant onset delay in effecting such treatment and avoids on-off phenomena in such treatment, said oral dosage formulation consisting of said immediate release layer and said sustained release layer, said immediate release layer providing rapid onset to antiparkinson activity and said sustained release layer providing sustained antiparkinson activity.

29. A method for treating Parkinson's disease in a patient having need of such treatment consisting of orally administering at least one bilayer tablet to said patient, said tablet having a sustained release core layer consisting of 25-75 mg carbidopa, 100-400 mg levodopa, methocel, microcrystalline cellulose, croscarmellose sodium, silicon dioxide and magnesium stearate, and an immediate release outer layer over said sustained release core layer, said immediate release layer consisting of 10-25 mg carbidopa, 50-200 mg

levodopa, microcrystalline cellulose, croscarmellose sodium, silicon dioxide and magnesium stearate.

30. A method according to claim 29, wherein said immediate release outer layer consists of 25 mg carbidopa, 100 mg levodopa, 224 mg microcrystalline cellulose, 15 mg croscarmellose sodium, 3.0 mg silicon dioxide and 3.0 mg magnesium stearate, and said sustained release core layer consists of 50 mg carbidopa, 200 mg levodopa, 80 mg methocel, 61 mg microcrystalline cellulose, 15 mg croscarmellose sodium, 2.0 mg silicon dioxide and 2.0 mg magnesium stearate, the mg being mg/tablet.

31. A method according to claim 29, wherein said immediate release outer layer consists of 12.5 mg carbidopa, 50 mg levodopa, 123.5 mg microcrystalline cellulose, 2.0 mg silicon dioxide and 10 mg magnesium stearate, and said sustained release core consists of 37.5 mg carbidopa, 150 mg levodopa, 80 mg methocel, 53.5 mg microcrystalline cellulose, 2.0 mg silicon dioxide and 2.0 mg magnesium stearate, the mg being mg/tablet.